Advances in Proficiency Testing for Genetic Laboratory Sciences

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Sir William Osler, 1892

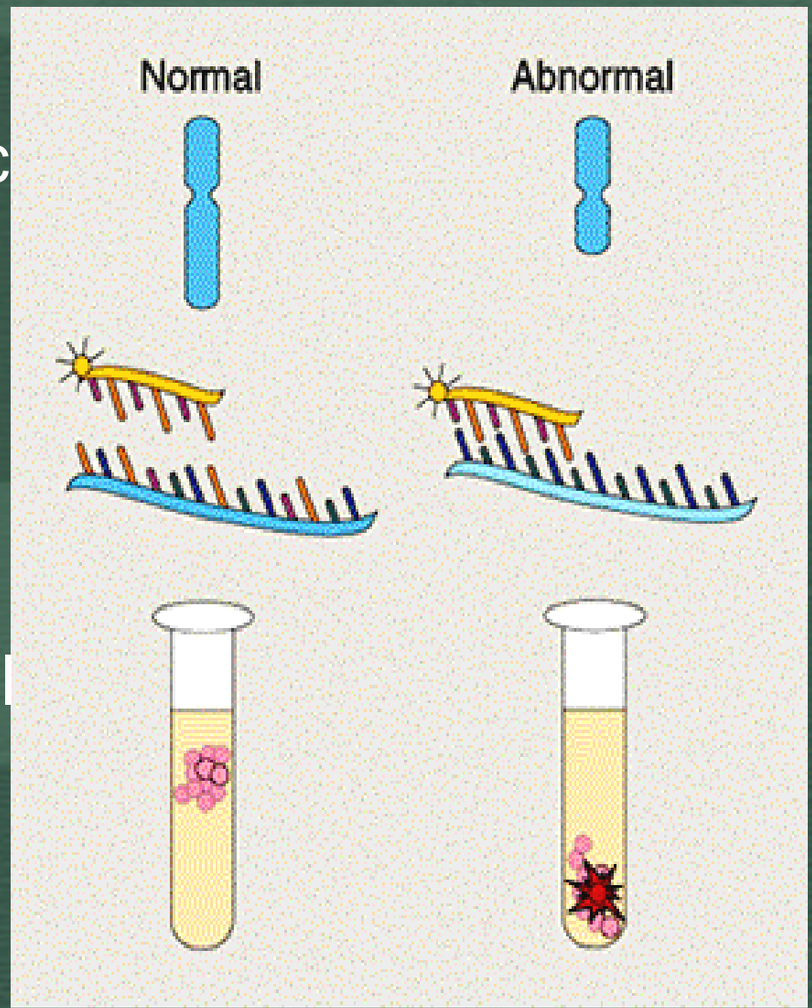
"If it were not for the great variability among individuals medicine might as well be a science and not an art"

Advances in Proficiency Testing for Genetic Laboratory Sciences

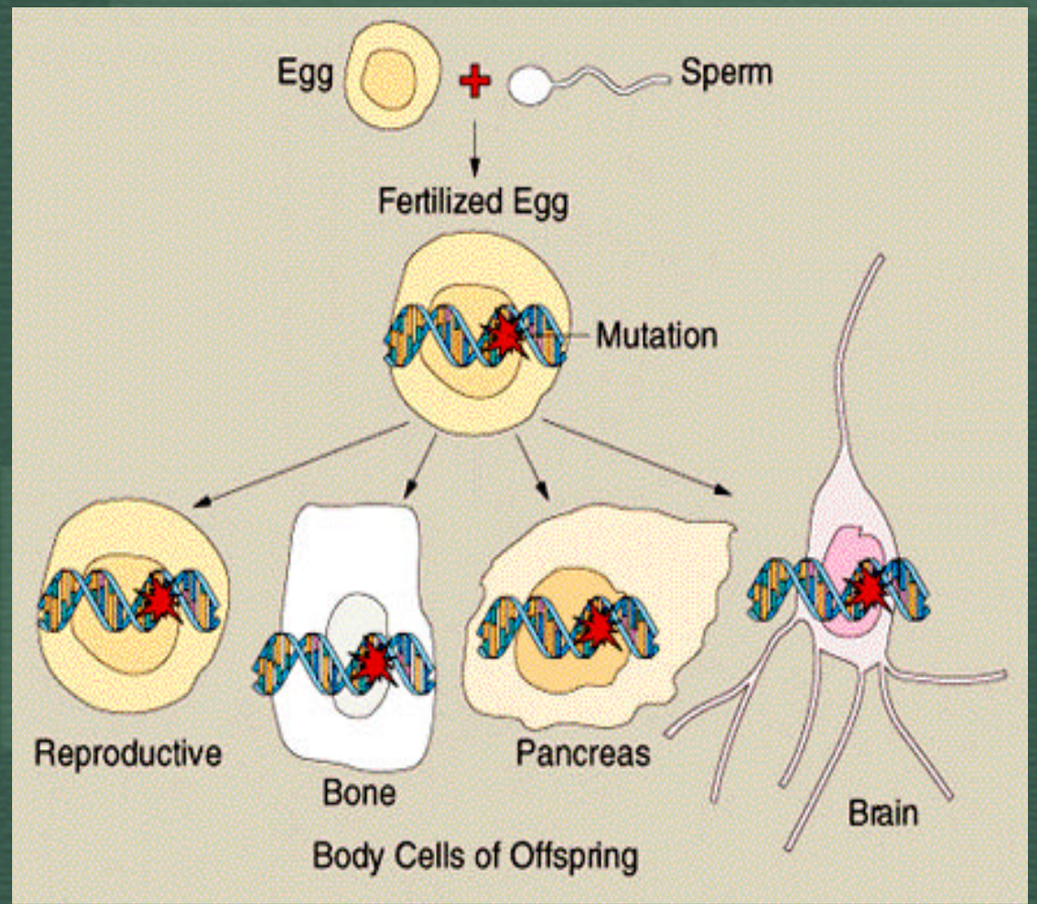
- Session Outline:
  1. Overview of genetic testing
  2. ACMG/CAP PT programs for genetic testing
  3. Challenges in genetic PT
  4. Logistical issues
  5. Economic challenges
  6. Conclusions

Three kinds of genetic tests

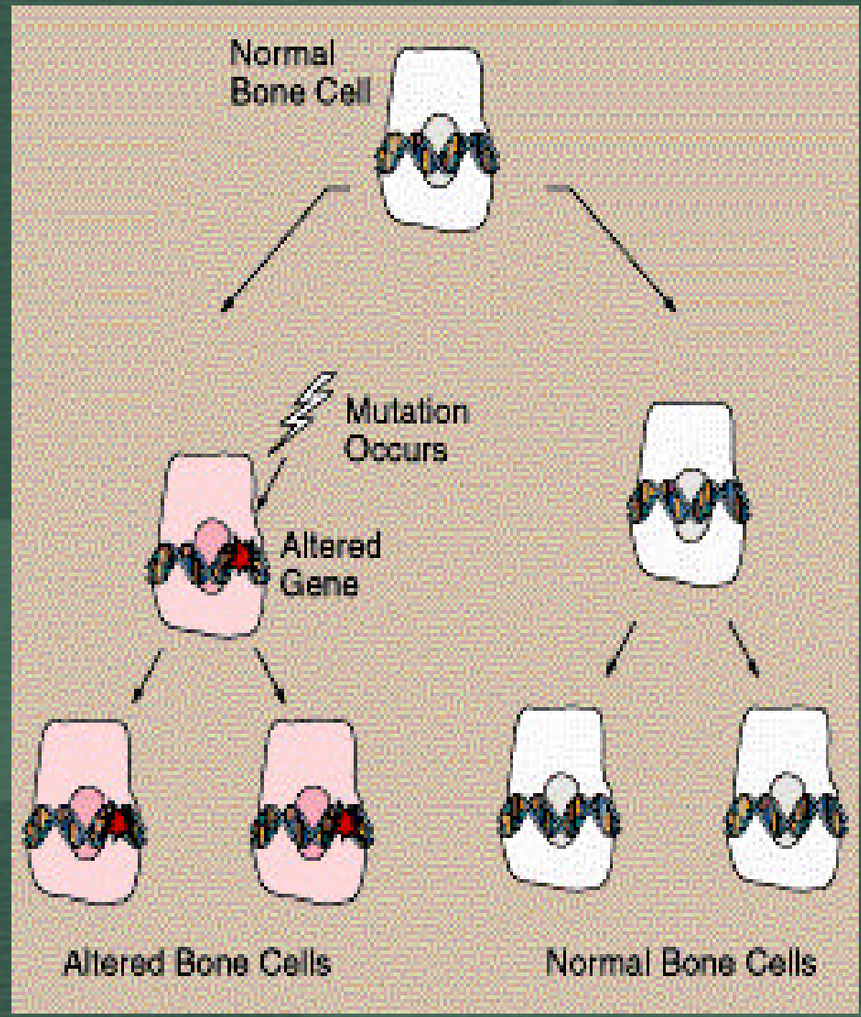
- Cytogenetic
- DNA
- Biochemical



Hereditary Mutations



Somatic Mutations



Value of Interlaboratory Comparison Program

- Provides reassurance of laboratory quality.
- Performance outside the norm can be identified and corrective action taken even when internal comparisons are consistent over time (good precision/poor accuracy).
- Comparative statistics may detect biases between different instruments/reagents/techniques.
- Overall statistics objectively reflect state of the art in laboratory practice, as opposed to arbitrary standards as set by outside agencies.

Types of Genetic PT Programs

- Formal
  - American College of Medical Genetics/College of American Pathologists (ACMG/CAP)
  - European Molecular Genetics Quality Network (EMQN)
  - Human Genetics Society of Australasia
- Informal
  - Interlaboratory exchange programs
    - GeneTests (www.genetests.org)
  - Regional programs
    - PacNoRGG
  - Professional organizations
    - ACMG
    - AMP
    - SIMD

CAP Proficiency Testing Program in Molecular Pathology

- Molecular Oncology (MO)
- In Situ Hybridization (ISH)
- Bacteria, Mycobacteria, Viruses (ID, HIV/HV2, HC5, HC6)
- Fluorescence In Situ Hybridization (CYF, CYG)
- Molecular Genetics (MGL)
- Forensic DNA Databases (DNA)
- Forensic Identity (FID)
- Parentage (PI)
- Molecular HLA-A, B, C Typing (ML)
- Molecular HLA-DR, DQ, DP Typing (DL)
- Bone Marrow Engraftment (ME)

ACMG/CAP Biochemical and Molecular Genetics Resource Committee

- CAP
  - Wayne Grody (MGL)
    - Chair
  - John Eckfeldt (BGL)
  - Jeff Kant (MGL)
  - Ron McGlennen (MGL)
  - Walter Noll (MGL)
  - Tim Stenzel (MGL)
- CAP Fellow
  - Shuji Ogino (CAP Fellow)
- ACMG
  - Brad Popovich (MGL)
    - Vice Chair
  - Robert Desnick (BGL)
  - Steve Goodman (BGL)
  - Bill Nyhan (BGL)
  - Tom Prior (MGL)
  - Karen Snow (MGL)
- AACC Liaison
  - Elizabeth Rohlfs

Committee Charge

1. Develop, maintain and enhance proficiency testing program to reflect the state of the art in both biochemical and molecular genetics
2. Function as a resource to a variety of CAP and ACMG committees and commissions
3. Develop an interface with various agencies and organizations concerned with defining and maintaining excellence in both biochemical and molecular genetics
4. Contribute to the continuing education of the members of the CAP and ACMG through Surveys, critiques, publications, and participation in CAP and ACMG education programs

MGL Survey History 2/2002

Disease	1995	1996	1997	1998	1999	2000	2001	2002
1. CF	A/B	B	A	A	A/B	A/B	A/B	A/B
2. DMD/BMD	A	A	A	A	A	A/B	A/B	A/B
3. FreidreichÕs Altaxia			B			A	B	A/B
4. FVL			A	A	A	A/B	A/B	A/B
5. Fragile X	B	A	B	B	A/B	A/B	A/B	A/B
6. Hb S/C	B	B				A	A	A/B
7. Hemochromatosis				B	B	A/B	A/B	A/B
8. HD		A/B	B	B	B	B	B	A/B
9. Mytonic Dystrophy			A			A	A	A/B
10. Prothrombin					B	A/B	A/B	A/B
11. PWS/AS			B	B	B	B	B	A/B
12. RhD				A		A	A	A/B
13. SCA					A	B	B	A/B
14. SMA					A	A/B	A	A/B
15. MTHFR						A/B	A/B	A/B
16. BRCA1/2							A	A/B
17. MEN2							B	A/B

MGL Enrollment

Year	Participant Number		
1998	136		
1999	173		
2000	198		
2001	217		
2002	204	101	14

Demographics of MGL-B 2001

- MGL-B 2001
  - 217 participating labs
  - 192 responses received
- US = 143
- International = 74

- Countries represented
  1. South Africa
  2. Brazil
  3. Canada
  4. Japan
  5. Australia
  6. Germany
  7. Chile
  8. Singapore
  9. South Korea
  10. France
  11. US

MGL Program 1998-2002
Challenges per year (# of samples/challenge)

Disease	1998	1999	2000	2001	2002
1. DMD	1(3)	1(2)	2(3)	2(3)	2(3)
2. CF	1(3)	2(2)	2(3)	2(3)	2(3)
3. HbS/C			1(3)	1(3)	2(3)
4. FRAX	1(3)	2(2)	2(3)	2(3)	2(3)
5. Huntington (HD)	1(3)	1(2)	2(3)	1(3)	2(3)
6. FVL	1(3)	1(2)	2(3)	2(3)	2(3)
7. DM1			1(3)	1(3)	2(3)
8. PWS/AS	1(3)	1(2)	1(3)	1(3)	2(3)
9. Friedreich			1(3)	2(3)	2(3)
10. RhD	1(3)		1(3)	1(3)	2(3)
11. HFE (HLA-H)	1(3)	1(2)	2(3)	2(3)	2(3)
12. Prothrombin		1(2)	2(3)	2(3)	2(3)
13. SCA		1(2)	1(3)	1(3)	2(3)
14. SMA		1(2)	2(3)	1(3)	2(3)
15. Methylenetetrahydrofolate Reductase Deficiency (MTHFR)				2(3)	2(3)
16. BRCA 1/2				1(3)	2(3)
17. MEN2				1(3)	2(3)

PROPOSED SPECIMEN MODULARIZATION ACMG/CAP PT PROGRAM

Thrombophilla Module	Common Mutation Module	Red Blood Cell Module	Trinucleotide Repeat Module	Neurogenetics Module
FVL	FraX	HbS/C	SCA-1	SMA
PTH	CF	RhD	SCA-2	DMD
MTHFR	HFE	BRCA1/2	HD	MD

MGL-B 2001 Participation / Disease

- 217 Total Participants
- 192 Responses Received

Disease/Analyte	2001(B)
1. DMD	22
2. CF	45
3. HbS/C	A
4. FRAX	85
5. Huntington (HD)	25
6. FVL	152
7. DM1	A
8. PWS/AS	37
9. Friedreich ataxia	13
10. RhD	A
11. HFE (HLA-H)	85
12. Prothrombin	134
13. SCA	11
14. SMA	A
15. Methylenetetrahydrofolate Reductase Deficiency (MTHFR)	98
16. BRCA 1 & 2	
17. MEN2	12

ADOPTED SPECIMEN MODULARIZATION ACMG/CAP PT PROGRAM 2002

- 17 Analytes
- 3 Specimens per challenge
- 2 times /year

Module 1	Module 2	Module 3
FV	CF	BRCA1
PT	DMD/BMD	BRCA2
MTHFR	FA	MEN2
FX	HD	
PW/AS	DM	
HH	RhD/E	
	HbA/C	
	SMA	
	SCA	

Participant Costs for MGL and Modularization

- Costs:
  - 2000 $812
  - 2001 $1,200
  - 2002: Modules introduced
    - #1 $800
    - # 2 $1,000
    - # 3 $850
- Modules ultimately designed to keep PT costs lowest for the majority of participants

Participation and Enrollment Fees for 2002 ACMG/CAP PT Program

	Module 1	Module 2	Module 3
	FVL	CF	MEN2
	PT	DMD/BMD	BRCA1
	MTHFR	FA	BRCA2
	FX	HD	
	PW/AS	DM	
	HH	RhD	
		HbA/C	
		SMA	
		SCA	
Number of Participants	**204**	**101**	**14**
Enrollment Fee	**$800**	**$1,000**	**$850**

MGL Grading Started in 2001

- =10 responses necessary for grading
- Grading based on 80% consensus
- Grading for presence or absence of:
  - Proper allele (SNPs): CF, FV, PT, etc.
  - Exons: DMD, SMA, etc.
  - Mutational status (i.e. genotype/phenotype interpretation): SCA, FX, DM, HD, etc.
- Alleles not (yet) graded for some analytes, examples:
  - Fragile X: FRAXA
  - MEN2: RET

Grading Criteria
Questions and Challenges

- Is the 80% rule acceptable for labs performing germ line genetic testing?
- Should PT performance be “coupled” to lab accreditation?
- Should the ACMG and CAP be proactive in educating MGL participants?
  - Should special emphasis be placed on labs with sub-optimal performance?

Special Challenges in Providing PT for Genetic Testing

- Lack of validated control materials
  - ATCC
  - Coriell
  - Other cell repositories

Select Genetic Diseases with Characterized Mutations Available

Coriell Cell Repository

Disease	Number of Cell Lines Available with Defined Mutations	Number of Unique Allelic Variants
Apolipoprotien A	20	3
Hereditary Breast and / Ovarien Cancer • BRCA1 • BRCA2)	 24 6	 20 6
Cystic Fibrosis	74	40
Dentatorubral-Pallidoluysian Atrophy	3	3
Duchenne Muscular Dystrophy	11	7
Factor V Leiden Mutation	4	1
Familial Adenomatous Polyposis	32	4
Fragile X Syndrome	26	21
Friedrich Ataxia	10	10
Gaucher Disease	10	4
Hemoglobin S	3	1
Hereditary Hemochromatosis	26	2
Huntington Disease	15	14
Medium Chain Acyl-CoA Dehydrogenase Deficiency	10	1
Methylenetetrahydrofolate Deficiency Therolabile Variant	4	2
Multiple Endocrine Neoplasia Type 2A	2	2
Myotonic Dystrophy	31	4
Factor II Thrombohpilia	2	2
RhD Genotyping	2	1
Spinal Muscular Atrophy	2	2
Spinocerebellar Ataxia • Type 1 • Type 3	 2 2	 2 2
Tay-Sachs Disease	11	5

Special Challenges in Providing PT for Genetic Testing

- Lack of validated control materials
  - ATCC
  - Coriell
  - Other cell repositories
- Lack of any control materials for some analytes
  - CF

ACMG Recommended CF Mutation Panel

- ACMG 25 Mutation Panel based on >0.1%frequency world wide

ΔF508	R553X	R1162X	2184delA	3120+1G>A
ΔI507	G542X			
621+1G>T	R117H	1717-1G>A	A455E	
G85E	R334W	R347P		
1078delT	3849+10kbC>T	2789+5G>A	3659delC	I148T

Available via Coriell

Not available via Coreill

- 2 CDC grants awarded to address lack of appropriate control materials

Conclusions

- Standards and Guidelines: CRITICAL
  - Enable “coupling” of PT with accreditation
  - Must be quickly adaptable in fast moving field such as genetic testing
- Lab inspectors must be knowledgeable
  - Should board certification be required for inspectors?
- Should ordering physicians be able to access relevant PT results for genetic testing?
- EDUCATION, EDUCATION, EDUCATION!!!

Conclusions

- Enlightened
- Thank you